UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte CHUN-MING CHEN, CHARLES R. CARPENTER, HAOYI GU and ALI NAQUI

Appeal No. 2004-1734
Application No. 08/942,369

HEARD: March 10, 2005

ELLIS, GRIMES and GREEN, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of 20-24, 26 and 31-43, all the claims pending in the application. Claims 1-19, 25 and 27-30 have been canceled.

Claims 20, 26, 38 and 43 are representative of the subject matter on appeal and read as follows:

> 20. A method of detecting the presence of urinary pathogens in a biological sample and of simultaneously determining the susceptibility of the urinary pathogens to antimicrobial agents, said method comprising:
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> providing a multicompartment assay device comprising:
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> at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; at least one compartment comprising a uropathogenic specific medium; and, at least one compartment comprising an antimicrobial susceptibility interpretation medium;
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> placing a portion of the biological sample respectively in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; said at least one compartment comprising a uropathogenic specific medium; and, said at least one compartment comprising an antimicrobial susceptibility interpretation medium comprising an antimicrobial agent;
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> whereby metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms indicates the presence of microbial organisms in a sample; metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising a uropathogenic specific medium indicates the presence of urinary pathogens in the sample; and metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising an antimicrobial susceptibility interpretation medium indicates that the organisms lack susceptibility to the antimicrobial agent comprised in said antimicrobial susceptibility interpretation medium; and
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> examining the compartments to determine the presence of urinary pathogens in said biological sample and the susceptibility of said urinary pathogens to said antimicrobial agents.
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> 26. The method of claim 20 wherein the at least one antimicrobial susceptibility interpretation medium comprises amoxicillin, clavulanic acid/amoxicillin, or enrofloxacin.

38. A method of detecting the presence of urinary pathogens in a biological sample and of simultaneously determining the susceptibility of the urinary pathogens to antimicrobial agents, said method comprising:

providing a multicompartment assay device comprising:

at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; at least one compartment comprising a uropathogenic specific medium comprising yeast extract; and, at least one compartment comprising an antimicrobial susceptibility interpretation medium;

placing a portion of the biological sample respectively in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; said at least one compartment comprising a uropathogenic specific medium comprising yeast extract; and, said at least one compartment comprising an antimicrobial susceptibility interpretation medium comprising an antimicrobial agent;

whereby metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms indicates the presence of microbial organisms in a sample; metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising a uropathogenic specific medium comprising yeast extract indicates the presence of urinary pathogens in the sample; and metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising an antimicrobial susceptibility interpretation medium indicates that the organisms lack susceptibility to the antimicrobial agent comprised in said antimicrobial susceptibility interpretation medium; and

examining the compartments to determine the presence of urinary pathogens in said biological sample and the susceptibility of said urinary pathogens to said antimicrobial agents.

43. The method of claim 38 wherein the at least one antimicrobial susceptibility interpretation medium comprises amoxicillin, clavulanic acid/amoxicillin, or enrofloxacin.

The examiner relies on the following references:

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| Libman et al. (Libman) | 4,046,138 | Sep. 6, 1997 |
| Johnson | 4,077,845 | Mar. 7, 1978 |
| Brocco | WO 94/16097 | Jul. 21, 1994 |
| Odaka et al. (Odaka) | JP 04-051890 | Feb. 20, 1992 |

Thaller et al. (Thaller), "New Plate Medium for Screening and Presumptive Identification of Gram-Negative Urinary Tract Pathogens," Journal of Clinical Microbiology, vol. 26, pp. 791-793 (1988).

The claims stand rejected as follows:

I. Claims 20-24 and 31-36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson in view of Libman and Thaller.

II. Claims 38-42 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson in view of Libman, Thaller and Odaka.

III. Claims 26 and 37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson in view of Libman, Thaller and Brocco.

IV. Claim 43 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson in view of Libman, Thaller, Odaka and Brocco.

We reverse all four rejections.

Background

According to the appellants, bacterial-urinary tract infections are common human and veterinary diseases. Brief, p. 2. The primary causative agents are said to be the primary gram-negative organisms which include E. coli, Klebsiella spp., Enterobacter spp., Proteus mirabilis, Proteus vulgaris, Morganella morganii, Providencia reterri, Acinetobacter spp. and Enterococcus faecalis. Id.

As indicated by the claims above, the present invention is directed to a method of detecting the presence of a urinary tract infection and its susceptibility to an antimicrobial agent. The appellants state that this is accomplished, in part, by the use of a uropathogenic-specific medium. Brief, p. 2. According to the appellants, said medium

> allows only the growth of the primary urinary Gram-negative pathogens and allows for substantially less growth of any other bacteria of a biological matrix (specification, p. 12, line 11 et seq.; p. 19, Table 1). The specification defines the primary Gram-negative urinary pathogens as the group of bacteria which cause at least 85-90% of the human and veterinary urinary tract infections (specification, p. 10, line 19 et seq.) [emphases omitted]. Brief, p. 2.

The invention involves a multi-compartment assay device which comprises a first compartment containing a medium capable of sustaining the growth of the total microorganisms in a urine sample; a second compartment containing a uropathogenic-specific medium; and a third compartment containing the uropathogenic-specific medium and an antimicrobial agent. According to the appellants, the present invention differs from previous methods in that it enables one to collect a non-sterile urine

sample and make a simultaneous determination of the presence and susceptibility of any primary Gram-negative uropathogens present in said sample. Brief, pp. 3-4. That is, because contaminating flora are normally present on a patient's skin, an animal's fur, or in the environment, the collection of a urine specimen for analysis often results in the specimen being contaminated by bacteria, or otherwise being collected in a non-sterile manner. Brief, p. 2. The present invention is said to avoid this problem by employing a uropathogenic-specific medium which only enables the growth of primary gram-negative uropathogens and not other bacteria present in a biological sample.

Discussion

In reviewing the applied prior art we find that Johnson discloses a microtiter-type device (a multicompartment assay device), for exposing a test sample to a variety of test reactants. Johnson, the abstract; col. 1, lines 6-11. The device contains dehydrated reagents which can be rehydrated with aliquots of the inoculum to be tested. Id., the abstract; col. 2, lines 28-35. Johnson further discloses that the device can be used to determine the sensitivity of microorganisms to antibiotics. Id., col. 1, lines 5-11; col. 2, lines 9-11 and lines 35-44; col. 3, lines 25-29. Johnson still further discloses that

> In accordance with the present invention, a self-contained rehydratable microtiter type device is disclosed in which serial concentrations of material can be predeposited and dried in multiple growth wells or cavities of the device and then a preselected aliquot amount of a chosen inoculum from a reservoir in the device is used to rehydrate the dried material to a proper liquid concentration. Following incubation, if any, the results are observed. For example, by rehydrating dried antimicrobial agents microbial sensitivity can be determined by

> macroscopically observing turbid growth. Thus, specimen can be introduced into selective culture mediums and known antibiotics. The optical characteristics will change if (a) the specimen contains a microorganism which is favored by the culture medium of the blend and (b) the microorganism is not susceptible to the antibiotic. Johnson, col. 2, lines 28-44.

Johnson still further discloses the use of said device to test for pathogens found in urinary tract infections. Johnson, col. 3, lines 25-39; col. 7, lines 37-40 and lines 44-46. To that end, Johnson states (col. 3, lines 30-37), inter alia:

> . . . it is possible to analyze selectively for the following organisms which account for the vast majority of pathogens found in urinary tract infections: Pseudomonas aeruginosa, Proteus spp., Citrobactor freundii, Serratia spp., Escherichia coli, Klebsiella/Enterobacter, Yeasts, Enterococcus Group D, Staphylococcus aureus

Johnson still further discloses that

> It is desirable to have at least one of the growth wells contain only culture medium by itself. Culture medium in the remaining wells can have antibiotics blended with it. The antibiotics can vary from well to well and two different wells can have the same antibiotics, but at different strengths [col. 7, lines 10-15].
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> In accordance with the invention, pathogens can be detected, identified, grouped and enumerated rapidly using specimens directly for inoculation of selective media. The selective media can be freeze-dried and especially formulated for specific organisms commonly encountered in clinical urine specimens. In addition, positive controls are possible and all the growth wells are reconstituted simultaneously in aliquot amounts. Growth in individual growth wells permits a positive test for indication of organisms [col. 7, lines 34-43].

Libman discloses a device for collecting body fluids which is said to be especially convenient for taking mid-stream urine samples. Libman, the abtract, col. 1, line 66- col. 2, line 3. Libman still further discloses the use of "two or more different media, selective and non-selective, adjacent to one another, thereby achieving the

important feature of presumptive identification of pathogens in a single culturing." Id., col. 3, lines 64-67. According to Libman:

> The preferred agars we use are CLED agar and MacConkey Agar or EMB Agar. CLED agar (Cystine Lactose Electrolye Deficient Agar) is ideal in enumerating and presumptively identifying urinary flora. It supports growth of urinary pathogens and contaminants. Additionally, the lack of electrolytes prevents a common culturing problem - swarming of Proteus. Organisms can be presumptively identified by color of colonies and media and/or morphology of colonies. MacConkey Agar and EMB Agar are well-known differential media for detection and isolation of enteric microorganisms. MacConkey and EMB agars have been used in hospitals for many years. The common gram negative organisms (responsible for more than 90% of urinary tract infections) can be identified readily with MacConkey Agar and EMB Agar [col. 3, line 67- col. 4, line 15].

Thaller discloses a selective, differential medium (T-mod) for screening common gram-negative urinary tract pathogens. Thaller, the abstract; p. 791, col. 1, para. 2. In tests of E. coli, P. mirabilis, K. pneumoniae, Serratia marcescens, Citrobacter freundii and Pseudomonas aeruginosa, Thaller reports no significant difference in the colony counts and sizes between the T-mod and MacConkey media. Id., p. 791, col. 2, paras. 2-3. Thaller further reports that in tests of 267 infected urine samples, the T-mod media presumptively identified 248 gram-negative strains. Id., p. 792, col. 1, first complete para. According to Thaller, T-mod medium "provides good presumptive identification of the gram-negative rods most frequently involved in urinary tract infections. Id., para. 2.

Odaka discloses a culture medium for the proliferation of coliform bacteria that exist in food, pharmaceuticals, cosmetics, drinking water and urine. Odaka, p. 3.

Odaka reports that a rapid method of bacterial growth is achieved using a culture media which contains, inter alia, 4-methyl-umbelliferyl-β-galactoside (4-MUGal) and yeast extract. Id., pp. 3 and 4. According to Odaka the 4-MUGal is changed to 4-methyl-umbelliferon (4-MU) in the presence of galactose which generates a readily detectable fluorescence. Id., p. 4.

Brocco discloses an antibiotic assay for urinary pathogens which comprises seventeen (17) dried antibiotics, which include inter alia, amoxicillin and clavulanic acid, in various wells of a microtiter device. Brocco, pp. 4 and 10.

Rejection I

The examiner argues that it would have been obvious to one of ordinary skill in the art

> to include the nonselective medium of Libman in the method of Johnson where the motivation would have been to provide a positive control for the microbial growth, as suggested by Johnson. It would also have been obvious to use the selective medium of Thaller as the selective medium in the method of Johnson where the motivation would have been to "analyze very selectively" for organisms causing an infection (Johnson, col. 3, lines 31-35) in order to presumptively identify the causative organism in order to determine an appropriate course of treatment, as suggested by both Libman (col. 2, lines 48-53) and Johnson (col. 3, lines 30-39). One would also have been motivated to use the selective medium of Thaller in the method of Johnson and Libman because it is an improvement over other selective medium such as that taught by Libman. [Answer, pp. 5-6].

It is well established that the examiner has the initial burden under 35 U.S.C. § 103 to establish a prima facie case. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785,

787-88 (Fed. Cir. 1984). To that end, it is the examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available in the art, would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 745 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

We commend the examiner for his thoroughness in briefing this case, but even assuming, arguendo, that we agree with each component of his argument as to why the applied prior art would have rendered the present invention obvious, we would still be unable to sustain the rejection. The problem here is that the examiner has not addressed each limitation present in the claims. Thus, the examiner has not considered the invention as a whole. In re Ochiai, 71 F.3d 1565, 1569, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); Jones v. Hardy, 727 F.2d 1524, 1529, 220 USPQ 1021, 1025 (Fed. Cir. 1983); W.L. Gore & Associates Inc., v. Garlock, Inc., 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

First, we find that the examiner relies on Libman for disclosing the use of non-selective media. However, we do not find, and the examiner has not pointed out, any teachings or suggestion in Libman, Johnson or Thaller to include a signal-generating substrate which is metabolized in said media in the manner described in representative claim 20.

Second, we find that the examiner relies on Johnson for disclosing a medium which is indicative of the antibiotic sensitivity of pathogens found in a urinary tract

infection. However, we do not find, and the examiner has not pointed out, any teachings or suggestions in Johnson, Libman or Thaller to employ a uropathogenic-specific media, and a signal-generating substrate which is metabolized, in the reservoir containing the antibiotic.

Thus, since the examiner has not addressed two important limitations present in the claims, we are compelled to reverse the rejection.

Rejection II

The examiner argues, with respect to claims 38-42, that it would have been obvious to one of ordinary skill in the art

> to have added the yeast extract of Odaka to the medium in the method of Johnson, Libman and Thaller where the motivation would have been to enhance growth of E. coli and allow for more rapid detection of uropathogens as taught by Odaka. [Answer, p. 7].

Here, we find that the examiner relies on Odaka solely for its teachings with respect to adding yeast extract to media employed in the method set forth in representative claim 20. Since Odaka does not make up for any of the deficiencies discussed above with respect to the teachings of Johnson, Libman and Thaller, it reasonably follows that this rejection fails for the reasons set forth for representative claim 20.

Accordingly, Rejection II is reversed.

Rejections III and IV

Given the reasons set forth above as to why Johnson, Libman, Thaller and Odaka would have rendered the claimed method of simultaneously detecting target microorganisms in a biological sample and determining the susceptibility of the microorganisms to antimicrobial agents, the examiner argues that it would have been further obvious to one of ordinary skill in the art to include the amoxicillin and clavulanic acid disclosed by Brocco as antimicrobial agents in the method taught by Johnson, and that "the motivation would have been to test susceptibility of microorganisms, specifically urinary pathogens/E. coli, to any known antibiotic or mixture of antibiotics, as suggested by Johnson, in order to determine an appropriate course of treatment for a subject infected with the microorganisms." Answer, p. 9.

Here, we find that the examiner relies on Brocco only for teaching the addition of amoxicillin and clavulanic acid to media in order to analyze the sensitivity of microorganisms to these antibiotics. However, since Brocco does not make up for the deficiencies discussed above with respect to the teachings of Johnson, Libman and Thaller, it reasonably follows that this rejection fails for the reasons set forth for Rejection I.

Accordingly, Rejections III and IV are reversed.

In view of the foregoing, the decision of the examiner is reversed.

REVERSED

JOAN ELLIS
Administrative Patent Judge )
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